REMARKS

Amendments to the claims

Claim 1-11 and 13 are cancelled. Claim 12 has been rewritten as an independent claim incorporating the substance of claims 1 and 13. New claims 21-28 incorporate the substance of canceled claims 2-9.

Claim 12 corresponds to the method claim as originally filed and further reflects the elected species cancer.

Claim 12 is amended to recite optional substituents. New claims 22, 23, 25 and 28 also recite the optional substituents. Support is found at the paragraph spanning pages 9 and 10.

Claim 15 was amended to place in independent form.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-9 and 16 stand rejected as anticipated by Abbas,[1] and by Dyachenko I[2] and II.[3] Claims 1-9 and 16 are cancelled. The rejection of claims 1-9 and 16 is moot.

Further Abbas and Dyachenko I and II are directed to synthetic chemistry and do not disclose any utility. Thus, (as recognized by the Office Action) none of the documents teach or suggest a method of treating cancer or the use of the compounds in a pharmaceutical composition.

Rejection Under 35 U.S.C. § 103

Claims 1-9 and 16 stand rejected as obvious over the combined teachings of Abbas, and

[1] Abbas *et al.*, J. Chemical Research, Synopses 4:124-125 (2001)).
[2] Dyachenko *et al.* Chemistry of Heterocyclic Compounds, 34: 188-194 (1998).
[3] Dyachenko *et al.*, Russian Journal of Organic Chemistry 33:1014-1017 (1997)).

by Dyachenko I and II. Claims 1-9 and 16-18 are canceled. The rejection of claims 1-9 and 16 is moot.

Further Abbas and Dyachenko I and II are directed to synthetic chemistry and do not disclose any utility. Thus, (as recognized by the Office Action) none of the documents teach or suggest a method of treating cancer or the use of the compounds in a pharmaceutical composition.

Rejection Under 35 U.S.C. § 112 ¶ 1 (written description)

Claim 1 stands rejected as lacking adequate description with respect to solvates and hydrates. To advance prosecution, claim 1 is canceled and its substance is incorporated into amended claim 12, which recites a method of treating a cancer mediated by excessive or inappropriate HSP90 activity in mammals. Claim 12 does not recite hydrates and solvates. Withdrawal of this rejection is requested.

Applicant does not consider that solvates and hydrates are different chemical forms of a compound of formula I. Instead, solvates and hydrates are different physical forms of the compound. Certainly a solvate or a hydrate of a compound of formula I still requires the compound of formula I, and therefore incorporates the invention defined by the now amended claims. Thus, one producing a solvate or hydrate of a compound of formula I makes use of that invention.

As the skilled practitioner recognizes, a hydrate is a molecule, for example the claimed molecule, in combination with a specific number of water molecules arranged in a particular fashion around the molecule. The solvate is a molecule, for example the claimed molecule,

associated with a specific number of solvent molecules arranged in a particular fashion around the claimed molecule. Regardless of the physical form, the compound is still present.

Rejection of Claim 1 Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claim 1 stands rejected as lacking enablement of solvates and hydrates of the compounds. Claim 1 is canceled and its substance incorporated into claim 12. Claim 12, as amended, does not recite solvates or hydrates. Withdrawal of this rejection is requested.

Rejection of Claims 1, 3, 5, 6, 9, and 10 Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claims 1, 3, 5, 6, 9, and 10 stand rejected as lacking enablement with respect to the scope of claimed compounds used to treat cancer. Office Action at page 8.

To advance prosecution, claims 1, 3, 5, 6, 9, and 10 are canceled. Amended claim 12 recites particular chemical groups that may be optional substituents. Amended claim 12 does not recite that R_4 may be a carboxylic ester. Withdrawal of this rejection is requested.

Rejection of Claims 12 and 13 Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claims 12 and 13 stand rejected as lacking enablement with respect to treatment of all cancers. Office Action at pages 10-12.

Amended claim 12 recites a method of treating a cancer mediated by excessive or inappropriate HSP90 activity in mammals by administering a compound of Formula I, or a salt or N-oxide thereof. Claim 13 is canceled.

To make an enablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*,

999 F.2d 1557, 1562 (Fed. Cir. 1993). The Patent Office has not met its burden with respect to claim 12.

The Patent Office first contends that claim 12 is not enabled because the function of HSP90 remains poorly understood. Office Action mailed January 16, 2009 at page 10. However, enablement does not require that the mechanism underlying an invention is known.

The Patent Office also contends that Xiao[4] teaches that HSP90 inhibitors "might be effective in killing end-stage tumors, but they might promote progression of early state tumors." Office Action mailed January 16, 2009 at pages 10 and 11. However, it is black letter law that even if a claim covers some inoperative embodiments, the claim is not necessarily invalid. *Atlas Powder Co., v. E.I. DuPont,* 750 F.2d 1569, 224 USPQ 414 (Fed. Cir. 1984). In any event, Xiao does not state that HSP90 inhibitors do promote early stage tumors. Rather, Xiao merely identifies a "potential" concern that they "might" do so. Page 1140, col. 2, ¶ 3. While Xiao offers hypothetical suggestions to explain the potential concern, no data is provided in support. In fact, Xiao states clearly that HSP90 inhibitors have demonstrated efficacy in cancer:

> Several Hsp90 inhibitors, such as 17-AAG, purine-scaffold derivatives and sheperdin, show very high selectivity for Hsp90 in tumor cells rather than in normal cells. 17-AAG has entered phase I/II clinical trials with very good effectiveness. Many other inhibitors are under preclinical development.

Page 1140, col. 2, ¶ 2 (emphasis added).

Xiao also concludes that HSP90 inhibitors are a recognized cancer treatment: "It is well-accepted in oncology that cancer treatment of any type, *including Hsp90 inhibitors*, may be harmful to the fetus of a pregnant woman suffering from cancer." Page 1141, paragraph spanning

[4] Xiao *et al.*, "Effectiveness of hsp90 inhibitors as anti-cancer drugs," Mini Rev Med Chem. 2006 Oct;6(10):1137-43.

col. 2 (emphasis in original).

The Patent Office cites Song[5] as supporting unpredictability with respect to Hsp90 inhibition because "the role of Hsp 90 inhibitors in pancreatic cancer has not been studied." Office Action at page 11. Song does not support the Patent Office's position. Song shows, as predicted, that HSP90 inhibitors inhibit pancreatic cancer both *in vitro* and *in vivo*:

> *In vitro*, we show that pharmacologic inhibition of Hsp90 by IPI-504 exerts anti-proliferative effects in a panel of pancreatic cancer cells in a dose- and time-dependent manner. In pancreatic cancer xenografts obtained directly from patients with pancreas cancer, the agent resulted in a marked suppression of tumor growth.

Song, page 3275, abstract.

Furthermore, both Xiao and Song emphasize that HSP90 activity is often excessive or inappropriate in cancers. Xiao states that "[w]hat makes Hsp90 especially promising as a target for anti-cancer drugs is that many of its client proteins are in signaling and chromatin-remodeling pathways, and these pathways are often disrupted in <u>many types of cancers</u>." Xiao, page 1137, abstract (emphasis added).

Song teaches that HSP90 is a good oncology target in multiple cancers because it regulates many proteins: "Targeting Hsp90 is an attractive strategy for anticancer therapy because the diversity and relevance of biological processes are regulated by these proteins in <u>most cancers</u>." Song, page 3275, abstract (emphasis added).

Finally, the specification also supports efficacy of HSP90 inhibitors in a variety of cancer models. HSP90 inhibitors "were shown to reverse the malignant phenotype of fibroblasts transformed by the v-Src oncogene (Uehara et al., 1985), and subsequently to exhibit potent

[5] Song *et al.*, "Antitumor activity and molecular effects of the novel heat shock protein 90 inhibitor, IPI-504, in pancreatic cancer," Mol Cancer Ther. 2008 Oct;7(10):3275-84.

antitumour activity both *in vitro* and *in vivo* animal models (Supko et al., 1995)." Specification at page 3 ¶ 4 to page 4 ¶ 1.

The Examiner has the burden of establishing a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). In this case, the Examiner has not met the burden of making a *prima facie* case that independent claim 12 and dependent claims 21-28 are not enabled for their full scope.

Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. § 112 ¶2

Claims 1, 3, 5, 6, and 9-11 stand rejected as indefinite because:

- The expressions hydrate, solvate, optional substituents, optionally substituted and carboxylic ester in claims 1, 3, 5, 6, 9, and 10 are indefinite.
- Claim 9's recitation of "R_4 represents $CONR^B(Alk)_nR^A$" lacks antecedent basis because claim 1 does not permit the carboxamide to be substituted.
- "R^C" lacks antecedent basis in claims 10 and 11.
- "R^B" and "R^C" are not defined in claim 1.

Office Action at pages 12-13.

To advance prosecution, claims 1, 3, 5, 6, and 9-11 are canceled. Amended claim 12 does not recite hydrate, solvate, or carboxylic ester. Claim 12 and new claims 22, 23, 25, and 28 each recite the optional substituents that may be substituted.

Applicants respectfully traverse the rejection that $CONR^B(Alk)_nR^A$ lacks antecedent basis. Formula $CONR^B(Alk)_nR^A$ is not an optional substitute of a carboxamide as the Patent Office asserts. Rather, the formula is a particular species of carboxamide. New claim 28

incorporates the substance of now-cancelled claim 9 and recites the method of claim 12 wherein R_4 is *a carboxamide group* of formula $-CONR^B(Alk)_nR^A$. Claim 12 recites that R_4 may be a carboxamide. Claim 12 thus provides antecedent basis for all carboxamide groups in the R_4 position. Claims 10 and 11 are canceled; therefore, the rejections based on "R^B" and "R^C" are moot.

Amended claim 12 and new claims 21-28 are definite.

Withdrawal of this rejection is requested.

CONCLUSION

All rejections having been addressed, applicants respectfully submit that the instant application is in condition for allowance, and respectfully solicit prompt notification of the same.

Respectfully submitted,

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